Summary of Global Risk Assessment Approaches for the Formaldehyde Science – General Approaches of the EU, Canada, WHO and the US

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Formaldehyde Science Invited Experts Workshop:

Understanding Potential Human Health Cancer Risk – From Data Integration to Risk Evaluation

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EU – ECHA (2012) Hazard/Risk Classification

- Carc 1B (H350): "May cause cancer"; "limited" human (NPC only); "sufficient" animals (NPC);
- Muta 2 (H341): "suspected of causing genetic defects"
- "Suspected germ cell mutagen" due to site of contact DPX genotoxicity
- "No convincing evidence of a carcinogenic effect at distant sites or via routes of exposure other than inhalation."
- Mode of Action:
  - "Common understanding formaldehyde causes tumors above a threshold concentration by mechanisms that are initiated by the cytotoxic effects and secondarily regenerative cell proliferation", …but
  - "…data does not allow firm conclusion on a threshold-mode of action"

WHO

- WHO/IPCS CICADS (Concise International Assessment Document; 2002)
  - Animal/human cancer: Only respiratory tract tumors fulfill causality criteria
  - Mode of Action: Carcinogenic hazard to humans "…under conditions that induce cytotoxicity and sustained proliferation."
  - Moderate to high confidence in data indicating an "obligatory role of regenerative proliferation" for nasal tumors, although mechanism is unclear.
- WHO IARC (2012)
  - Classification 1 – "Carcinogenic to humans" – "Sufficient" evidence in humans and animals (NPC); "small majority" for "sufficient" evidence of leukemias
  - Mode of Action: Cell replication in response to cytotoxicity promotes carcinogenicity; assumed genotoxic – "moderately supports" leukemias

Canada

- Priority Substances List Assessment Report (2001)
  - CEPA Schedule 1 “toxic”
  - DSL Low priority substance (already risk managed; risks below Canada population-level exposures)
  - Carcinogenic hazard to humans “…under conditions that induce cytotoxicity and sustained regenerative cell proliferation.”
    - Genotoxicity cannot be excluded as contributing mechansism
- Health based guidance value (2004)
  - Predicted risk at chronic exposure to 1.2 ppb = 2.3×10^{-10}

United States

- EPA IRIS, under revision
  - Sufficient evidence of causal association for NPC, all leukemias, myeloid leukemia and LHP as group in humans
  - Animals data provide strong support for NPC, but limited data for LHP cancers
  - For NPC, mutagenic MoA operating in conjunction with key event of formaldehyde cytotoxicity-induced cell proliferation
  - Lifetime cancer risk at 1 ppb = 1×10^{-4}
- NTP Report on Carcinogens (2011)
  - "Known to be a human carcinogen"
  - Sufficient evidence in humans: nasal and myeloid leukemias
  - Sufficient evidence in animals: multiple species, sites and routes
  - Mechanistic events plausible in humans, including genotoxicity

Occupational Exposure Assessments

- German MAK: 0.3 ppm TWA, momentary value of 1 ppm
  - Cancer classification 4: non-genotoxic; cell proliferation important to MoA
- SCOEL: 0.3 ppm TWA, 0.6 ppm STEL
  - Cancer classification Group C: genotoxic carcinogen with a MoA-based threshold
- ACGIH: 0.1 ppm TWA, 0.3 ppm STEL
  - Cancer classification A1: confirmed human carcinogen
- NIOSH: 0.016 ppm REL, 0.1 ppm STEL
  - Cancer classification: carcinogen
- OSHA: 0.75 ppm TWA, 2 ppm STEL
  - Cancer classification: potential to cause cancer

Mode of Action: Cytotoxicity causing regenerative cell proliferation in upper respiratory tract consistently identified

- Current MoA evaluations focused entirely on formaldehyde
- Little consideration of toxicity and carcinogenicity associated with chemicals extensively systemically metabolized to formaldehyde, and how such data might further inform the MoA
  - Methyl chloride
    - Weak male mouse carcinogen; non-carcinogen in rats
    - Liver, brain, and testis formaldehyde increased after inhalation exposure
    - Depletes glutathione, a key detoxification mechanism
  - Caffeine
    - Extensively demethylated to formaldehyde; daily 400 mg dose of caffeine liberates approximately 2 mmoles of formaldehyde (60 mg)